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M/EEG source analysis

Rik Henson

MRC CBU, Cambridge

(with thanks to Christophe Phillips, Jeremie Mattout, Gareth Barnes, Jean Daunizeau, Stefan Kiebel and Karl Friston)





- 1. Forward Models for M/EEG
- 2. Variational Bayesian Dipole Estimation (ECD)
- 3. Empirical Bayesian Distributed Estimation
- 4. Multimodal integration





1. Forward Models for M/EEG

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Forward Problem

m Model



Inverse Problem

Forward Problem: Physics

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Current density: Likelihood Orientation Location = tQuasi-static Maxwell's Equations: $\nabla \cdot E$ $= \frac{\rho}{\rho}$ Kirkoff's law: Е М $Y = \overline{\Phi}$ (EEG) Y = B (MEG) $\nabla \cdot i = 0$ Electrical potential $\times B$ MRC | Medical Research Council

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Forward Problem: Physics





f depends on: location (orientation) of sensors geometry of head conductivity of head (source space)

Can have analytic or numerical form...

Forward Problem: Head Models

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Concentric Spheres:

Pros: Analytic; Fast to computeCons: Head not spherical; Conductivitynot homogeneous

Boundary (or Finite) Element Models:

Pros: Realistic geometry Homogeneous conductivity within boundaries

Cons: Numeric; Slow Approximation Errors



Other approaches (for MEG): Fit local spheres to each sensor;MRC | Medical Research CouncilSingle shell, spherical approx (Nolte)

Forward Problem: Meshes

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3 important surfaces for BEMs are those with large changes in conductivity: Scalp (skin-air boundary) Outer Skull (bone-skin boundary) Inner Skull (CSF-bone boundary)

(Represented as tessellated triangular meshes)

Extracting these surfaces from an MRI is difficult, eg, because CSF-bone T1-contrast is poor (use PD?)...

A fourth important surface (for some solutions) is: Cortex (WM-GM boundary)

Extracting this surface from an MRI is very difficult because so convoluted (though FreeSurfer)...





Forward Problem: Canonical Meshes

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Rather than extract surfaces from individuals MRIs, why not warp Template surfaces from an MNI brain based on spatial (inverse) normalisation?

Recap: (Spatial Normalisation)

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Forward Problem: Canonical Meshes

Rather than extract surfaces from individuals MRIs, why not warp Template surfaces from an MNI brain based on spatial (inverse) normalisation?

Mattout et al (2007), Comp Int & Neuro



Canonical Template (Inverse-Normalised)

(Also provides a 1-to-1 mapping across subjects, so source solutions can be written directly to MNI space, and group-inversion applied; see later)

Given that surfaces are part of the forward model (m), can use the model evidence p(Y | m) to determine whether Canonical Meshes are sufficient Henson et al (2009), Neuroimage

Individual

Forward Problem: ECD vs Distributed

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For small number of Equivalent Current Dipoles (ECD) anywhere in brain: is linear in but non-linear in r $Y = f(\overset{\square}{r})\overset{\square}{j}$

For (large) number of (Distributed) dipoles with fixed orientation and location: is linear in r $Y = F(\begin{bmatrix} N & N & N \\ r_1 & r_2 & r_N \end{bmatrix})J$





- 1. Forward Models for M/EEG
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Inverse Problem: VB-ECD

Standard ECD approaches iterate location/orientation (within a brain volume) until fit to sensor data is maximised (i.e, error minimised). But:

- 1. Local Minima (particularly when multiple dipoles)
- 2. Question of how many dipoles?

With a Variational Bayesian (VB) framework, priors can be put on the locations and orientations (and strengths) of dipoles (e.g, symmetry constraints)



 $p(\vec{r}, \vec{j}, \lambda_r, \lambda_j, \lambda_e \mid m) = p(Y \mid \vec{r}, \vec{j}, \lambda_e, m) p(\lambda_e \mid m) p(\vec{r} \mid \lambda_r, m) p(\lambda_r \mid m) p(\vec{j} \mid \lambda_j, m) p(\lambda_j \mid m)$ $MRC \mid Medical Research Council Kiebel et al (2008), Neuroimage$

Inverse Problem: VB-ECD

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Maximising the (free-energy approximation to the) model evidence p(Y | m) offers a natural answer to question of the number of dipoles



Kiebel et al (2008), Neuroimage

Inverse Problem: DCM

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Dynamic Causal Modelling (DCM) can be seen as a source localisation (inverse) method that includes temporal constraints on the source activities



David et al (2011), Journal of Neuroscience





- 1. Forward Models for M/EEG
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Inverse Problem: Distributed

Given *p* sources fixed in location (e.g, on a cortical mesh)...

...linear Forward Model for MEG/EEG:

- $\mathbf{Y} = \mathbf{L}\mathbf{J} + \mathbf{E} \qquad \mathbf{E} \sim N(\mathbf{0}, \mathbf{C}^{(e)})$
- Y = Datan sensorsJ = Sourcesp >> n sourcesL = Leadfieldsn sensors x p sourcesE = Errorn sensors......draw from Gaussian covariance $C^{(e)}$

(Free orientations can be simulated by having 2-3 columns in *L* per location)

Fact that *p*>>*n* means under-determined problem (cf. GLM and ECD)... ...so some form of regularisation needed, e.g, "Weighted L2-norm"...

MRC Cognition and Brain Sciences Unit Inverse Problem: Standard L2-norm

 $\mathbf{Y} = \mathbf{L}\mathbf{J} + \mathbf{E} \qquad \mathbf{E} \sim N(\mathbf{0}, \mathbf{C}^{(e)})$

$$\mathbf{J} = \arg\min\{\left\|\mathbf{C}^{(e)^{-1/2}}(\mathbf{Y} - \mathbf{L}\mathbf{J})\right\|^{2} + \left\|\mathbf{W}\mathbf{J}\right\|^{2}\}$$

$$= (\mathbf{W}^T \mathbf{W})^{-1} \mathbf{L}^T [\mathbf{L} (\mathbf{W}^T \mathbf{W})^{-1} \mathbf{L}^T + \lambda \mathbf{C}^{(e)}]^{-1} \mathbf{Y}$$

"Tikhonov Solution"

 $||Y - LJ||^{2}$ *"L-curve" method* $\lambda = regularisation$ (hyperparameter) $||WJ||^{2}$

W = I "Minimum Norm" $W = DD^{T}$ "Loreta" (D=Laplacian) $W = diag(L^{T}L)^{-1}$ "Depth-Weighted" $W_{p} = diag(L_{p}^{T}C_{y}^{-1}L_{p})^{-1}$ "Beamformer" $W = \emptyset$

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Phillips et al (2002), Neuroimage

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Inverse Problem: Equivalent PEB

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Parametric Empirical Bayesian (PEB) 2-level hierarchical form:

 $\mathbf{Y} = \mathbf{L}\mathbf{J} + \mathbf{E}^{(e)} \qquad \mathbf{E}^{(e)} \sim N(0, \mathbf{C}^{(e)})$ $\mathbf{J} = \mathbf{0} + \mathbf{E}^{(j)} \qquad \mathbf{E}^{(j)} \sim N(0, \mathbf{C}^{(j)})$

Likelihood:

$$p(\mathbf{Y} | \mathbf{J}) = N(\mathbf{L}\mathbf{J}, \mathbf{C}^{(e)})$$

Prior:

 $p(\mathbf{J}) = N(0, \mathbf{C}^{(j)})$

Posterior:

 $p(\mathbf{J} | \mathbf{Y}) \propto p(\mathbf{Y} | \mathbf{J}) p(\mathbf{J})$

Maximum A Posteriori (MAP) estimate:

$$\hat{\mathbf{J}} = \mathbf{C}^{(j)} \mathbf{L}^T [\mathbf{L} \mathbf{C}^{(j)} \mathbf{L}^T + \mathbf{C}^{(e)}]^{-1} \mathbf{Y}$$

cf Classical Tikhonov:

 $(\mathbf{W}^T\mathbf{W})^{-1}\mathbf{L}^T[\mathbf{L}(\mathbf{W}^T\mathbf{W})^{-1}\mathbf{L}^T+\lambda\mathbf{C}^{(e)}]^{-1}\mathbf{Y}$

 $C^{(e)} = n \times n$ Sensor (error) $C^{(i)} = p \times p$ Source (prior) covariance



$$\Rightarrow$$
 C^(j) = (**W**^T**W**)⁻¹

Phillips et al (2005), Neuroimage

Inverse Problem: Covariance Components (Priors)

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Specifying (co)variance components (priors/regularisation):

$$\mathbf{C} = \sum_{i} \lambda_{i} \mathbf{Q}_{i}$$

- C = Sensor/Source covariance
- **Q** = Covariance components
- λ = Hyper-parameters

1. Sensor components, $\mathbf{Q}_{i}^{(e)}$ (error):

"IID" (white noise):



Empty-room:



sensors

2. Source components, $\mathbf{Q}_{i}^{(j)}$ (priors/regularisation):

"IID" (min norm):



Multiple Sparse Priors (MSP):



Friston et al (2008) Neuroimage

Inverse Problem: HyperPriors

When multiple Q's are correlated, estimation of hyperparameters λ can be difficult (eg local maxima), and they can become negative (improper for covariances)

To overcome this, one can:

1) impose positivity on hyperparameters:

 $\alpha_i = \ln(\lambda_i) \Leftrightarrow \lambda_i = \exp(\alpha_i)$

2) impose weak, shrinkage hyperpriors:

$$p(\boldsymbol{\alpha}) \sim N(\boldsymbol{\eta}, \boldsymbol{\Omega})$$
 $\boldsymbol{\eta} = -4$ $\boldsymbol{\Omega} = a\mathbf{I}, a = 16$



uninformative priors are then "turned-off" (cf. "Automatic Relevance Detection")

$$\alpha \to -\infty \Leftrightarrow \lambda \to 0$$

Henson et al (2007) Neuroimage

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Henson et al (2007) Neuroimage



Inverse Problem: Full (DAG) model

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Source and sensor space



Friston et al (2008) Neuroimage

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Inverse Problem: Estimation

 Obtain Restricted Maximum Likelihood (ReML) estimates of the hyperparameters (λ) by maximising the variational "free energy" (F):

$$\hat{\boldsymbol{\lambda}} = \max_{\boldsymbol{\lambda}} p(\mathbf{Y} \mid \boldsymbol{\lambda}) = \max_{\boldsymbol{\lambda}} F$$

2. Obtain Maximum A Posteriori (MAP) estimates of parameters (sources, J):

$$\hat{\mathbf{I}} = \max_{j} p(\mathbf{J} \mid \mathbf{Y}, \hat{}) = \max_{j} F$$

3. Maximal F approximates Bayesian (log) "model evidence" for a model, *m*:

$$\ln p(\mathbf{X} \mid m) = \lim \int p(\mathbf{Y}, \mathbf{G}, \mathbf{\Sigma} \mid m) d \quad d \quad \approx F(\ , \ , \) \qquad m = \{\mathbf{h}, \mathbf{Q}, \ , \ \}$$

$$F(\boldsymbol{\chi},\boldsymbol{\Sigma},\hat{\boldsymbol{\chi}}) \propto -\boldsymbol{\mathcal{G}}(\boldsymbol{Y}\boldsymbol{Y}^{T}) - \boldsymbol{\mathbb{I}}\boldsymbol{\mathbb{C}} | \boldsymbol{\mathcal{G}}(\hat{\boldsymbol{\eta}} \quad \boldsymbol{\mathcal{Y}}^{T} \quad \boldsymbol{\bar{\alpha}}^{1}(\hat{\boldsymbol{\eta}} \quad \boldsymbol{\boldsymbol{\eta}} + \boldsymbol{\mathbb{I}}\boldsymbol{\Sigma}\boldsymbol{\boldsymbol{\Omega}}^{\hat{\boldsymbol{\chi}}^{-1}} | \boldsymbol{\boldsymbol{\Omega}}$$
Accuracy
Complexity

(...where \hat{a} and $\hat{\Sigma}$ are the posterior mean and covariance of hyperparameters)

Friston et al (2002) Neuroimage

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Inverse Problem: Multiple Sparse Priors

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Hyperpriors allow the extreme of 100's source priors, or MSP



$$G(\sigma) = [q_1, \dots, q_N] = \sum_{i=0}^{8} \frac{\sigma^i}{i!} A^i \approx \exp(\sigma A)$$



sources

#

sources

Hyperpriors allow the extreme of 100's source priors, or MSP



Friston et al (2008) Neuroimage

Inverse Problem: PEB Summary

Summary:

- Automatically "regularises" in principled fashion...
- ...allows for multiple constraints (priors)...
- ...to the extent that multiple (100's) of sparse priors possible (MSP)...
- ...(or multiple error components or multiple fMRI priors)...
- ... furnishes estimates of model evidence, so can compare constraints





- 1. Forward Models for M/EEG
- 2. Variational Bayesian Dipole Estimation (ECD)
- 3. Empirical Bayesian Distributed Estimation
- 4. Multi-modal and multi-subject integration

Multi-subject Integration (Group Inversion)

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Specifying (co)variance components (priors/regularisation):

$$\mathbf{C} = \sum_{i} \lambda_{i} \mathbf{Q}_{i}$$

- *C* = Sensor/Source covariance
- Q = Covariance components
- λ = Hyper-parameters

1. Sensor components, $Q_i^{(e)}$ (error):

"IID" (white noise):



Empty-room:



2. Source components, $Q_i^{(j)}$ (priors/regularisation):

"IID" (min norm):



Multiple Sparse Priors (MSP):



Friston et al (2008) Neuroimage

Multi-subject Integration (Group Inversion)

MRC Cognition and Brain Sciences Unit

Specifying (co)variance components (priors/regularisation):

 $\mathbf{C} = \sum_{i} \lambda_{i} \, \mathbf{Q}_{i}$

- *C* = Sensor/Source covariance
- Q = Covariance components
- λ = Hyper-parameters

1. Sensor components, $Q_i^{(e)}$ (error):

"IID" (white noise):

sensors





2. Optimise Multiple Sparse Priors by pooling across subjects $Q_i^{(j)}$



Multi-subject Integration (as before)



Source and sensor space



Multi-subject Integration





Multi-subject Integration: Leadfield Alignment

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Concatenate data across subjects

$$\begin{bmatrix} \tilde{\mathbf{A}}_{1} \tilde{\mathbf{Y}}_{1}, \dots, \tilde{\mathbf{A}}_{s} \tilde{\mathbf{Y}}_{s} \end{bmatrix} = \begin{bmatrix} \tilde{\mathbf{A}}_{1} \tilde{\mathbf{L}}_{1}, \dots, \tilde{\mathbf{A}}_{s} \tilde{\mathbf{L}}_{s} \end{bmatrix} \begin{bmatrix} \mathbf{J}_{1} \\ \mathbb{X} \\ \mathbf{J}_{s} \end{bmatrix} + \begin{bmatrix} \mathbf{E}_{1}^{(1)}, \dots, \mathbf{E}_{s}^{(1)} \end{bmatrix}$$

...having projected to an "average" leadfield matrix

$$\mathbf{A}_{i}\mathbf{L}_{i} = \mathbf{\tilde{L}}: \mathbf{\tilde{L}} = \langle \mathbf{A}_{i}\mathbf{L}_{i} \rangle_{i} \quad s.t.: \quad \mathbf{A}_{i} = \max \arg \left\{ |\mathbf{\tilde{L}}\mathbf{\tilde{L}}^{T}| \right\}: tr(\mathbf{\tilde{L}}\mathbf{\tilde{L}}^{T}) = n$$

Common source-level priors:

$$\mathbf{C}^{(j)} = \sum \lambda_k^{(j)} \mathbf{Q}_k^{(j)}$$

Subject-specific sensor-level priors:

$$\mathbf{C}_{i}^{(e)} = \sum \lambda_{ik}^{(e)} \mathbf{A}_{i} \mathbf{Q}_{k}^{(e)} \mathbf{A}_{i}^{T}$$

Multi-subject Integration: Results

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MMN





SPM {T₁₀}



MSP



SPM {T₁₀}

MSP (Group)







- 1. Symmetric integration (fusion) of MEG + EEG
- 2. Asymmetric integration of M/EEG + fMRI
- 3. Full fusion of M/EEG + fMRI?


Daunizeau et al (2007), Neuroimage



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Daunizeau et al (2007), Neuroimage

1. Symmetric integration (fusion) of MEG + EEG

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Symmetric Integration of MEG+EEG

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Specifying (co)variance components (priors/regularisation):

$$\mathbf{C} = \sum_{i} \lambda_{i} \mathbf{Q}_{i}$$

- C = Sensor/Source covariance $p(\mathbf{X}) = N(\mathbf{m}, \mathbf{C})$ Q = Covariance components
- λ = Hyper-parameters

1. Sensor components, $\mathbf{Q}_{i}^{(e)}(\text{error})$:

"IID" (white noise):



Empty-room:



2. Source components, $\mathbf{Q}_{i}^{(j)}$ (priors/regularisation):



Friston et al (2008) Neuroimage

Symmetric Integration of MEG+EEG

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Specifying (co)variance components (priors/regularisation):

$$\mathbf{C}_{i}^{(e)} = \sum_{j} \lambda_{ji}^{(e)} \mathbf{Q}_{ij}^{(e)}$$

1. Sensor components, $\mathbf{Q}_{ij}^{(e)}$ (error):

E.g, white noise for 2 modalities:



 $Q_{ij} = j$ th component for *i*th modality $\lambda_{ii} =$ Hyper-parameters



2. Source components, $\mathbf{Q}_{i}^{(j)}$ (priors/regularisation):





Multiple Sparse Priors (MSP):



Single Modality (as before)





Source and sensor space

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Symmetric Integration of MEG+EEG

• Stack data and leadfields for *d* modalities:



(note: common sources and source priors, but separate error components)

• Where data / leadfields scaled to have same average / predicted variance:

$$\dot{Y}_{i} = \frac{Y_{i}}{\sqrt{\frac{1}{m_{i}}tr(Y_{i}Y_{i}^{T})}} \qquad \tilde{L}_{i} = \frac{L_{i}}{\sqrt{\frac{1}{m_{i}}tr(L_{i}L_{i}^{T})}} \qquad m_{i} = \text{Number of spatial modes}$$
(e.g, ~70% of #sensors)

ERs from 12 subjects for 3 simultaneously-acquired Neuromag sensor-types:



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Symmetric Integration of MEG+EEG

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Faces - Scrambled, 150-190ms

EEG







IID noise for each modality; common MSP for sources (fixed number of spatial+temporal modes)

Symmetric Integration of MEG+EEG

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- Fusing magnetometers, gradiometers and EEG increased the conditional precision of the source estimates relative to inverting any one modality alone (when equating number of spatial+temporal modes)
- The maximal sources recovered from fusion were a plausible combination of the ventral temporal sources recovered by MEG and the lateral temporal sources recovered by EEG
- (Simulations show the relative scaling of mags and grads agrees with empty-room data)

1. Symmetric integration (fusion) of MEG + EEG

- 2. Asymmetric integration of M/EEG + fMRI
- 3. Full fusion of M/EEG + fMRI?

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Specifying (co)variance components (priors/regularisation):

$$\mathbf{C} = \sum_{i} \lambda_{i} \mathbf{Q}_{i}$$

C = Sensor/Source covariance $p(\mathbf{X}) = N(\mathbf{m}, \mathbf{C})$ Q = Covariance components

 λ = Hyper-parameters

1. Sensor components, $Q_i^{(e)}$ (error):

"IID" (white noise):







2. Source components, $Q_i^{(j)}$ (priors/regularisation):

"IID" (min norm):



Multiple Sparse Priors (MSP):



Friston et al (2008) Neuroimage

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Specifying (co)variance components (priors/regularisation):

 $\mathbf{C} = \sum_{i} \lambda_{i} \mathbf{Q}_{i}$

C = Sensor/Source covariance $p(\mathbf{X}) = N(\mathbf{m}, \mathbf{C})$ Q = Covariance components λ = Hyper-parameters

1. Sensor components, $Q_i^{(e)}(\text{error})$:

"IID" (white noise):





sensors

2. Each suprathreshold fMRI cluster becomes a separate prior $Q_i^{(j)}$

"IID" (min norm):

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Source and sensor space



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Henson et al (2010) Hum. Brain Map.

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SPM{F} for faces versus scrambled faces, 15 voxels, p<.05 FWE



5 clusters from SPM of fMRI data from separate group of (18) subjects in MNI space

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(binarised, variance priors)

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(binarised, variance priors)

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(binarised, variance priors)

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3.2 Fusion of MEG+fMRI (Application)

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(binarised, variance priors)

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(binarised, variance priors)

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IID sources and IID noise (L2 MNM)













None

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IID sources and IID noise (L2 MNM)







Gradiometers







Electrodes







None



Global

3.2 Fusion of MEG+fMRI (Application)

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IID sources and IID noise (L2 MNM)



fMRI priors counteract superficial bias of L2-norm

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IID sources and IID noise (L2 MNM)



fMRI priors counteract superficial bias of L2-norm

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NB: Priors affect variance, not precise timecourse...

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- Adding a single, global fMRI prior increases model evidence
- Adding multiple valid priors increases model evidence further Helpful if some fMRI regions produce no MEG/EEG signal (or arise from neural activity at different times)
- Adding invalid priors does not necessarily increase model evidence, particularly in conjunction with valid priors
- Can counteract superficial bias of, e.g, minimum-norm
- Affects variance but not not precise timecourse

- 1. Symmetric integration (fusion) of MEG + EEG
- 2. Asymmetric integration of M/EEG + fMRI
- 3. Full fusion of M/EEG + fMRI?

Fusion of fMRI and MEG/EEG?





Henson (2010) Biomag

Fusion of fMRI and MEG/EEG?

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Fixed Variable

Fusion of fMRI and MEG/EEG?

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Overall Conclusions

- SPM offers standard forward models (via FieldTrip)... (though with unique option of Canonical Meshes)
- 2. ...but offers unique Bayesian approaches to inversion:
 - 2.1 Variational Bayesian ECD
 - 2.2 Dynamic Causal Modelling (DCM)
 - 2.3 A PEB approach to Distributed inversion (eg MSP)
- 3. PEB framework in particular offers multi-subject and (various types of) multi-modal integration



The End

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Forward Problem: Physics



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Inverse Problem: Simulations

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Multiple constraints: Smooth sources (Q_s) , plus valid (Q_v) or invalid (Q_i) focal prior



Mattout et al (2006)

Inverse Problem: Simulations

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Multiple constraints: Smooth sources (Q_s) , plus valid (Q_v) or invalid (Q_i) focal prior

	Log-Evidence	Bayes Factor
Q _s	205.2	7047
Q _s ,Q _v	214.1	
Q _s , Q _v , Q _i	214.7	
(Q _s ,Q _i)	204.9	(1/9899)







Mattout et al (2006)

Inverse Problem: Temporal

$$\widetilde{Y} = LJ + E \qquad \begin{array}{c} E \sim N(0, V^{(e)} \otimes C^{(e)}) \\ J \sim N(0, V^{(j)} \otimes C^{(j)}) \end{array}$$

 $C^{(e)}$ = spatial error covariance over sensors $V^{(e)}$ = temporal error covariance over sensors $C^{(j)}$ = spatial error covariance over sources $V^{(j)}$ = temporal error covariance over sources

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In general, temporal correlation of signal (sources) and noise (sensors) will differ, but can project onto a temporal subspace (via S) such that:

$$S^T V_e S = S^T V_j S = S^T V S$$

V typically Gaussian autocorrelations...

 $V = KK^{T}$ $K(\tau)_{ij} = \exp\left(-\frac{(i-j)^{2}}{2\tau^{2}}\right)$ $\tau \sim 4ms$

then turns out that EM can simply operate on prewhitened data (covariance), where Y size *n x t*:

$$\hat{\lambda} = EM(\frac{1}{N_r}YS(S^TVS)^{-1}S^TY^T, Q)$$
$$\hat{J} = MYSS^T$$

Friston et al (2006)

Inverse Problem: Temporal

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Friston et al (2006)









true source



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3.2. Fusion of MEG+fMRI



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fMRI hyperparameters

Multi-subject Integration: Results

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MMN + 3 fMRI priors



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MMN + 3 fMRI priors (Group)





Henson et al (2011) Frontiers